HUK Study no 12/64

CENTER FOR INDOOR AIR RESEARCH
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APPLICATION FOR RESEARCH CONTRACT

1. PRINCIPAL INVESTIGATOR. NAME, TITLE, TELEPHONE # AND MAILING ADDRESS.

Tel: 44 423 500011
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(A) NAME: Mr Keith Phillips
(B) TITLE: Manager
(C) TELEPHONE #/ FAX #:
(D) DEPARTMENT: Analytical Chemistry
(E) INSTITUTION: Hazleton UK
(F) MAILING ADDRESS: Otley Road, Harrogate
(G) STATE/ZIP: North Yorkshire HG3 1P

2. PROJECT TITLE. Determination of personal exposures to Environmental Tobacco Smoke in British non-smokers

3. KEY WORDS. PLEASE PROVIDE THREE (3) KEY WORDS WHICH WILL BE USED AS REFERENCE HEADINGS. Environmental Tobacco Smoke

4. INSTITUTION. NAME AND ADDRESS OF INSTITUTION RESPONSIBLE AND ACCOUNTABLE FOR DISPOSITION OF FUNDS AWARDED ON THE BASIS OF THIS APPLICATION.

(A) INSTITUTION: Hazleton UK
(B) STREET ADDRESS: Otley Road
(C) CITY: Harrogate
(D) STATE/ZIP: North Yorkshire HG3 1PY

5. LOCATION. LIST LOCATION WHERE RESEARCH WILL BE CONDUCTED *IF OTHER THAN INSTITUTION IDENTIFIED IN #4 ABOVE.*

(A)

(B)

6. INCLUSIVE DATES AND TOTAL COSTS OF THIS SPECIFIC PROJECT RELATED TO EACH 12 MONTH PERIOD IF MORE THAN ONE YEAR IS REQUIRED TO COMPLETE PROJECT. SUMMARIZE FROM BUDGET PAGE, ITEM 12(J). IT MUST BE UNDERSTOOD THAT AWARDS FOR 2ND AND 3RD PERIODS ARE DEPENDENT ON CENTER APPROVAL OF CONTINUATION APPLICATION.

	Inclusive Date		Total Cost
(A) 1ST 12 MONTH PERIOD	September 1992	THRU August 1993	$ 125,000-00 POUNDS STERLING
(B) 2ND 12 MONTH PERIOD IF REQUIRED	-	THRU -	$
(C) 3RD 12 MONTH PERIOD IF REQUIRED		THRU	$

7. INSTITUTIONAL OFFICER. NAME, TITLE AND TELEPHONE NUMBER OF INDIVIDUAL AUTHORIZED TO SIGN FOR THE INSTITUTION IDENTIFIED IN #4 ABOVE. IT IS UNDERSTOOD THAT THE OFFICER, IN APPLYING FOR A CONTRACT, HAS READ AND FOUND ACCEPTABLE THE CENTER'S MANAGEMENT OF RESEARCH CONTRACTS AND CONTRACT ADMINISTRATION POLICY. (other than the payment schedule)*

(A) NAME: Mr M Wilson
(B) TITLE: Contracts Administrator
(C) TELEPHONE: 44 423 500011
(D) SIGNATURE OF INSTITUTIONAL OFFICER:
(E) DATE: 7 September 1992

10 ☒ PRELIMINARY STUDIES*. Page 8
(A) FEASIBILITY OF PROPOSED RESEARCH
(B) QUALIFICATIONS OF INVESTIGATOR

11 ☒ EXPERIMENTAL PLAN*. Page 9
(A) DESIGN
(B) METHODS
(C) ANALYSIS OF DATA
(D) INTERPRETATION OF RESULTS
(E) TIMETABLE FOR THE INVESTIGATION
(F) LITERATURE CITED

12 ☒ AVAILABLE FACILITIES AND RESOURCES. Page 13

8. AIMS - Page 5

9. SIGNIFICANCE OF PROPOSED WORK - Page 6
(a) Background
(b) Literature
(c) Identification of gaps in proposed researc area
(d) Project importance

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* APPEND AS MUCH MATERIAL AS REQUIRED. TYPE, SINGLE SPACE. USE 8-1/2" X 11" WHITE PAPER AND LABEL EACH SHEET WITH NAME OF THE PRINCIPAL INVESTIGATOR IN THE UPPER RIGHT HAND CORNER AND PAGE NUMBER AT THE BOTTOM. CONSECUTIVELY NUMBER EACH ADDENDUM BEGINNING WITH PAGE 5. DO NOT INSERT PAGES BETWEEN PAGES 1 AND 6, E.G., 2A, 2B, 3A, ETC. INCLUDE NINE COPIES AND AN ORIGINAL. IF SENDING PHOTOGRAPHS, INCLUDE 2 ORIGINAL SETS. NOTE: EACH OF THE NINE COPIES *MUST* BE PLACED IN A BINDER PER MAILING INSTRUCTIONS.

* Please see preferred method of payment on Hazleton Quotation.

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12.BUDGET. Detailed specific needs for the first 12-month period. Estimate category sub-totals for 2nd and 3rd periods, if required. Append justifications.

(a) Salaries, List personnel by name and title. Indicate individuals % time to be spent on this project.	$ 1st period	$ 2nd period	$ 3rd period
% Professional:			
% Technical:			
% Other:			
Fringe benefits payable at institution's rate of %			
Category (a) Sub-Total			
(b) Consultants (per diem, travel & expenses):			
Category (b) Sub-Total			
(c) Supplies & Expense: Consumables (by category)			
Animals and related costs			
Other expenses (itemize)			
Category (c) Sub-Total			
(d) Travel Expenses:			
Category (d) Sub-Total			
(e) Alterations and Renovations			
Category (e) Sub-Total			
(f) Sub-contracts			
Category (f) Sub-Total			
(g) Equipment			
Category (g) Sub-Total			
(h) TOTAL DIRECT COSTS			
(i) Indirect costs not to exceed 25% of the sum of (a) thru (f):			
(j) TOTAL PROJECT COSTS			

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13. **BUDGET**

	Pounds Sterling
Pilot Study (10 volunteers)	7,500
Main Study (minimum of 280 volunteers)	
• Volunteer recruitment, administration, reimbursement	24,500
• Collection/delivery of kits; equipment maintenance	9,500
• Analytical phase, to include method development/ validation and routine analysis of samples for total particulates, nicotine, UVPM/FPM, solanesol and salivary cotinine	75,000
• Prepare a report and a manuscript for publication	8,000
TOTAL	**125,000**

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14 12. BIOGRAPHICAL SKETCH of all professional personnel listed in 12(a). Append. Please include the following: Name, title, education, scientific field, major research interest, research and/or professional experience and publications. (Limit list of publications to the 20 most important and/or relevant.)

See Appendix C

15 13. a) Are HUMAN SUBJECTS to be used in this research? _____ Yes _____ No
If yes, attach Institutional Review Board approval for procedures involving human subjects.

See Appendix D

b) Are LABORATORY ANIMALS to be used in this research? _____ Yes _____ No
If yes, attach Institutional Animal Care and Use Committee approval for procedures involving animals.

Not applicable

16 14. SIGNATURE OF PRINCIPAL INVESTIGATOR: It is understood that the applicant in applying for a Contract has read and found acceptable the Statements of Policy and Terms Under Which Project Contracts Are Made appearing in the application package. **(other than payment schedule)**

K. Phillips — 12 August 1992

Signature of Principal Investigator — Date

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8 AIMS

The broad objective of the proposed work is to determine, through a variety of inter-related measures, the extent of exposure to ETS in typical British non-smokers.

The specific aims of the project are as follows:

1. To determine, in non-smoking British volunteers, the range and median levels of 24 hour exposure to nicotine and to ETS-related particulates.

2. To assess the contribution of exposure to ETS from different environments such as homes, the workplace and leisure and travel situations.

3. To assess whether non-smokers who are married to smokers have significantly higher exposures to ETS than non-smokers married to non-smokers.

4. To evaluate the extent of correlation between the different methods of exposure determination; questionnaires, salivary cotinine measures and personal monitoring of exposures to airborne constituents.

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9. SIGNIFICANCE OF PROPOSED WORK

a) Background

Two approaches have been used to assess whether there is any risk associated with exposure to ETS. One is based on epidemiology and the other based on the quantities of smoke constituents to which non-smokers are exposed. Further information is required on typical exposure levels in order to address questions relating to epidemiology studies and to obtain a better assessment of how much ETS people are exposed to.

Most of the information about the exposure of non-smokers to ETS is based on measurements of ETS levels in **locations** such as homes, offices and restaurants with assumptions about the time spent in these locations. There have been several such studies, particularly in the USA, but not enough to characterise properly the range of ETS exposure of non-smokers. It is, therefore, important to obtain further information for a variety of other situations, including different countries with various climates and lifestyles.

Surprisingly, there have, until recently, been few attempts to measure exposure of **people** directly as they go about their normal lives, moving from location to location, even though this approach should provide more realistic results than those calculated from ETS levels in various locations. Although this personal monitoring technique has been common practice in the industrial hygiene field for several years, it is only recently that the analytical methodology has been refined sufficiently to allow ETS measurements to be carried out by this approach. A few ETS exposure studies of this type have now been completed or are underway.

Nevertheless, further studies in a variety of countries are still required in order to obtain sufficient information with which to address some of the important ETS issues.

Although levels of both nicotine and ETS particles have been determined in several studies of **locations**, personal monitoring studies have tended to measure nicotine but not particles. In view of the limitations of nicotine as a marker for ETS and the importance often attached to particles, there clearly is a need for complementary personal monitoring studies in which ETS particles are also measured, especially now that the UVPM (ie. ETS particulate matter measured by ultra-violet light), FPM (ie. ETS particulate matter measured by fluorescence) and solanesol methods are available for estimating the ETS contribution to total particles.

A criticism of existing epidemiological studies of ETS is that they failed to include a direct measure of exposure level. Spousal smoking has frequently been used as an index of exposure in these studies but the validity of this approach is open to question. It is, therefore, important to determine whether reported extent of spousal smoking correlates with directly measured exposure. For the same reasons, it would be useful to determine how well directly measured ETS exposure can be predicted by questionnaire or by measurements of salivary cotinine since these approaches are also used as an alternative to direct measurements. It would also be useful to establish how peoples' personal assessment of their exposure compares with their measured exposure.

Smoking bans are being introduced in the workplace and in various public leisure and travel situations. It would be helpful to obtain further information on the extent of exposure in these situations to assess how each contributes to overall exposure.

The Study proposed here will help to address these issues.

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b) Literature

Perhaps the most extensive published evaluation of data related to ETS exposure is the monograph recently published by Guerin et al (Guerin, Jenkins and Tomkins, The Chemistry of Environmental Tobacco Smoke: Composition and Measurement, Lewis Publishers Inc. 1992). In this review of the existing literature, fourteen field studies of nicotine levels and twenty three field studies of particulate levels were tabled. Only one these studies referred to data acquired in the United Kingdom and so there is little to base comparisons in the literature between the predominately US based literature and a United Kingdom situation.

The same monograph briefly discusses the literature related to personal monitoring and biomarker assays. One personal monitoring study (Proctor et al, Environmental International 17, 287-297) measured personal exposures to nicotine and measured salivary cotinine levels in non-smoking British women. This study suggested a lack of correlation between cotinine and nicotine exposure levels. However, the study was small (50 subjects) and made no assessment of particulate exposures. US data on particulates (Spengler et al, Environmental Science and Technology, 19, 700-706, 1985) reported that 24 hour exposures to particulates were around 40 ug/m3 higher in those living in smokers' homes compared to non-smokers homes'. However, these researchers used comparative location techniques rather than chemical apportionation to determine the ETS contribution to particulates.

c) Identification of gaps in proposed research area

Our proposal addresses several gaps in the literature pertaining to the issue of population exposure to ETS. These are:

1. The sparsity of data specific to the United Kingdom. As far as we are aware there is only one UK based published study that has attempted to resolve the issues addressed in our proposal. Because of this it is uncertain whether the larger US database can be applied to the UK.

2. Little or no data exist on particulate exposure directly related to ETS as measured by chemical apportionation techniques.

3. The comparison of exposure assessment techniques (questionnaires versus chemical monitoring versus biomarker measurements) has rarely been addressed in studies measuring more that two of these comparative measures. The proposed study would compare six different measures (questionnaire, nicotine exposure, UV-PM exposure, Fluorescence-PM exposure, solanesol and salivary cotinine).

d) Project importance

Several agencies are currently considering the potential effects of exposure to ETS. In the United Kingdom, the Independent Scientific Committee on Smoking and Health stated it its Fourth report published in 1988 that it is recognised that the whole area of investigation of the composition and concentration of ETS is a difficult one and that it would keep the issue under review as new research findings became available. UK specific data would presumably be of value to this committee. On a broader basis, the investigation should prove useful in terms of an example of the use of personal monitoring techniques for investigating exposures to substances found in the environment.

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10 PRELIMINARY STUDIES

a) Feasibility of the proposed research

A novel active monitoring device, which allows the simultaneous collection of airborne nicotine and particulates has been devised for this experiment. The effectiveness of this device has been evaluated in controlled experiments and we are confident that the collection technique will appropriately represent the personal exposures. The design and function of this device is described fully in the experimental plan. Apart from this, all of the methods proposed are standard and appear in the peer-reviewed literature.

b) Qualifications of investigator

The curriculum vitae of all the key investigators are appended to this proposal. The Institution, Hazleton UK, is experienced both in subject interview techniques and in the analysis if environmental and biological samples.

A profile of the company is attached to this proposal.

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11 EXPERIMENTAL PLAN

a) Design

The following is a brief description of the study design. 300 non smokers will be randomly selected from an existing database of 11,000 subjects held by GHBA/Hazleton Clinics in Leeds UK.

Either five or six volunteers will be studied each day such that eleven subjects will be studied every two days, including weekends. Each volunteer will be monitored for a continuous period of 24 hours.

The volunteers will all be from Yorkshire in the North of England, and will be selected to be representative in terms of age, sex and locality (urban/rural).

Their exposure to nicotine, TSP, UV-PM (particulates measured by UV light) F-PM (particulates measured by fluorescence) and solanesol will all be monitored.

At the beginning and the end of the monitoring period, saliva samples will be taken. The volunteers will maintain a diary throughout the monitoring period. A questionnaire will be completed at the end of the 24 hour period.

Prior to the start of the main study (approximately 3 to 4 weeks) a "pilot study" or trial will be conducted using ten volunteers. The purpose of the trial is to assess all aspects of the main study including collection, analysis and questionnaire completion and to highlight any problems that might occur in the main study.

b) Methods

i) Subjects

300 non-smokers will be randomly selected from an existing database of 11,000 subjects held by GHBA/Hazleton Clinics in Leeds, UK. All volunteers are to be non-smokers aged between 20 and 60 years of age. Subjects will reside in the Leeds and Harrogate area in the North of England and they will be distributed based on age, sex and locality (urban/rural).

A pre-acceptance questionnaire will be used to select an excess of volunteers so that in the event of drop-outs suitable replacement candidates can be selected. The volunteers will be provided a financial incentive for their involvement in the study.

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ii) **Sample delivery and collection**

A minimum of 280 volunteers results are required. To acheive this, five or six subjects will be monitored daily producing 11 samples every two days over a period of fourteen consecutive days. Thus 70 results will be obtained in a two week period. This regime will be repeated on three consecutive occasions.

The personal monitors will be delivered to the volunteers at pre-determined locations and times and will be collected as close as possible to 24 hours later. The monitor pump will be turned on and off by the investigators and not by the subjects. Times of start and finish, as well as recorded cycles of the pumps, will be recorded.

Saliva samples will be taken from each subject at the beginning and at the end of the 24 hour sampling period.

Questionnaires will be completed by the investigator who will ask a series of pre-determined questions, coded for later analysis. These questions will be asked at the end of the sampling period. The volunteers will also carry a time-activity diary in order to record observations throughout the monitoring period.

iii) **Collection and analysis of airborne nicotine and particulates**

The collection of these analytes relies upon the use of a compact collection system which is worn by the subject in order to sample the air to which he/she is exposed. It consists of two filters in series connected to a sampling pump. The first filter collects the total particulates and the second, which is acid-treated, traps nicotine vapour.

Air is drawn through the filters by a small, quiet, battery powered pump which is concealed in a small bag worn at the subject's waist level. The pump is set at a flow rate of 139 ml/min so that a total volume of 200 litres is drawn through the pump during the 24 hour monitoring period.

The filter holder is attached to a rigid wire "necklace" which holds the monitor in place and allows ease of removal. A clip will be provided as an alternative to the necklace.

During periods of sleep or bathing the monitor will be taken off but be placed close to the subject. Such events will be noted in the time-activity diary.

In brief, the analytical methods to be used are as follows:

The analysis of the nicotine and 3-Ethenylpyridine contained on the acid treated filter involves extraction into dis-isopropyl ether (DIPE) (containing 0.1m/l triethylamine and 2.0 mg/l N-ethylnornicotine (internal standard) from sodium hydroxide which is used to basify the filter.

The DIPE extract is then analysed by capillary gas chromatography with nitrogen specific detection.

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The total suspended particulate concentration is determined gravimetrically by the difference in weights of the front teflon pad before and after sampling.

After weighing, the pad is extracted in methanol in order to determine UV-PM, F-PM, solanesol and any residual nicotine and 3-Ethenylpyridine that might have been trapped on the front filter.

iv) Collection and analysis of saliva

Saliva will be collected from each subject immediately before and after each monitoring period. This will be achieved by the subject chewing on a dental swab for around a minute. The swab is then returned to the laboratory sealed in its salivette container.

The saliva is recovered by high speed centrifuge for two minutes. Cotinine and N-ethylnorcotinine (internal standard) are extracted from the saliva and the extract analysed by GC with mass selective detection.

v) Detection limits

Under the sampling regime described, the detection limits for the various analytes are expected to be as follows:

Total particulates	20 $\mu g/m^3$ as ETS particulates
UV-PM	5 $\mu g/m^3$ as ETS particulates
F-PM	5 $\mu g/m^3$ as ETS particulates
Solanesol	10 $\mu g/m^3$ as ETS particulates
Nicotine	0.5 $\mu g/m^3$
3-Ethenylpyridine	0.5 $\mu g/m^3$
Salivary cotinine	0.5 $\mu g/ml$

vi) Quality Control

The study will be performed where appropriate in accordance with the Good Laboratory Practice provided as guidelines of the UK Department of Health compliance programme (1989). Where appropriate all work will be performed under Hazleton's standard operating procedures.

Any deviations from the protocol will be recorded as a file note against the raw data and highlighted in the final report.

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c) **Analysis of data**

Subject information and corresponding analytical data will be compiled in a database as the study progresses.

Computation of means and ranges for each of the analytes and correlations between the different analytes will be achieved through standard statistical procedures.

d) **Interpretation of the results**

The results will be reported both as a detailed research findings report to the Center for Indoor Air Research and if the data allow, as a publication for a peer-review scientific Journal.

e) **Timetable of investigation**

Should approval be received, the pilot phase of the study could begin within one month. Field sampling would occur over a period of around two and one half months. Data analysis and reporting is expected to be complete three months after the completion of sampling.

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12 AVAILABLE FACILITIES AND RESOURCES

Hazleton UK is the European Headquarters of Hazleton Corporation, a wholly owned subsidiary of Corning Laboratory Services Inc. The company provides a wide range of product development and safety evaluation services to the pharmaceutical, agrochemical and chemical industries.

The laboratories at Harrogate, which occupy 185,000 square feet on a 20 acre site, are engaged in general and reproduction toxicology, molecular toxicology, metabolism and pharmacokinetics and biological and chemical analysis. The 50 bed GHBA/Hazleton Clinic, Leeds, undertakes clinical pharmacology studies in healthy volunteers and a variety of patient population groups.

All studies conducted by Hazleton and GHBA satisfy requirements for Good Laboratory and Good Clinical Practices (GLP and GCP) respectively.

Of the 625 staff, 159 are degree level and 39 doctorate level. Five percent of time is devoted to training, as part of the company's Total Quality Management programme.

The modern analytical laboratories are particularly well equipped to undertake the proposed study and the Principal Investigator has direct experience of tobacco smoke analysis studies.

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